UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/912,436	07/26/2001	Markku Michael Jeltsch	1064/48929	4856

23911 7590 01/09/2004

CROWELL & MORING LLP
INTELLECTUAL PROPERTY GROUP
P.O. BOX 14300
WASHINGTON, DC 20044-4300

EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	6

DATE MAILED: 01/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/912,436	JELTSCH ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5/15/02* .

4)☐ Interview Summary (PTO-413) Paper No(s). _____ .

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: .

Part III: Detailed Office Action

Claims 1-18 are pending and under consideration.

Formal Matters:

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. For example, see page 13. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because they both require a particular sequence, and require that that sequence be altered, that is, *not* be the recited sequence. Using claim 1 as an example, the claim has a sequence that may be SEQ ID NO: 1, 3 or 5, *and* "a nucleotide sequence encoding at least one putative N-glycosylation site inserted therein", so that it would no longer be SEQ ID NO: 1, 3 or 5. Language such as "consisting of a variant of SEQ ID NO: 1, 3 or 5 which consists of SEQ ID NO: 1, 3 or 5 which has been altered to add at least one putative N-glycosylation site" or the equivalent would be remedial.

The claims are also indefinite because of the recitation that the glycosylation site has been "inserted" into the protein. Art-accepted usage of the word "inserted" or "insertion" denotes a lengthening of the resultant molecule. However, the invention as disclosed is the result of substitution of amino acids to form a glycosylation site without lengthening the resultant molecule. While the goal can also be achieved by insertion of additional codons, such would seem to be limiting the invention to exclude the working example. As it is not clear what applicants intend by "inserting", the claims that recite such are indefinite.

Claim 1 is further indefinite because the metes and bounds of those nucleic acids that will hybridize to a given sequence are dependent upon the conditions used for hybridization and washing. The term "stringent conditions" is a relative term, and neither the claim nor the specification breathe life and meaning into the term to allow determination of the metes and bounds of the claims. It is noted that exemplary hybridization conditions are disclosed at page 13 of the specification, however said definition is incomplete, and is merely exemplary, and non-limiting.

Claim 15 is indefinite because it is not clear what is intended by "increasing an amount of a soluble VEGF"..."from a host cell"; amendment to replace "from" with "secreted by " or "produced by" would be remedial.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, 7, and 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to nucleic acids of unspecified structure. Claim 1 requires only that the claimed nucleic acid "hybridizes under stringent conditions" to a reference sequence, and have "at least one putative N-glycosylation site inserted therein". It is generally accepted in the art that only a limited stretch of identity is required for two sequences to hybridize under "stringent" conditions, commonly as little as 23 nucleotides, which is not sufficient to encode any significant conserved structural feature that would lend function to the encoded protein. Further, the claims have no functional limitations as to either the nucleic acid itself of any protein that might be encoded thereby. The specification, on the other hand, is clearly drawn to nucleic acids that encode a specific protein, VEGF-B, the sequence of which has been altered to

comprise one or more putative N-linked glycosylation sites, which sites are characterized by the amino acid sequence "NXT". There is no evidence of conception of an invention commensurate with the breadth being claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO: 1, 3 or 5, modified by the introduction of N-glycosylation sites, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-5, 7-13, and 15-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is the insertion of N-glycosylation sites in to VEGF-B. The state of the prior art, as discussed below, is that VEGF-B was known, that it was known that the protein was not glycosylated, that it was further known that glycosylation of VEGF-A increases recombinant production of the protein without affecting biological activity, and finally, it was known in the art how to introduce glycosylation sites into proteins, although it is not predictable whether or not a given glycosylation site will actually be glycosylated. The breadth of the claims, however, is extreme. The claims are not limited to proteins with VEGF activity, nor are they limited by particular structure, due to the inclusion of "hybridization" language in numerous of the claims. There is no structure nor function to be conserved by the protein or the nucleic acids, which themselves are not required , as in claim 1, to actually encode any protein. While the person of ordinary skill in the art would certainly know how to make glycosylated variants of VEGF-B and nucleic acids encoding such, and would further know how to use such, the specification does not provide adequate guidance as to how to make or use variants that are defined by "hybridization" language, nucleic acids that do not encode protein having VEGF activity, or proteins without VEGF function or having distinct but unspecified function. Accordingly, it would require undue experimentation to make and use the invention in a manner commensurate in scope with the claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11, and 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksson et al. (U.S. Patent Number 5,607,918) in view of Claffey et al. (BBA 1246:1-9, 1995) and Keyt et al. (U.S. Patent Number 6,020,473).

Eriksson et al. disclose VEGF-B. At figure 9, an alignment is provided, showing conservation among PDGF-A and -B, PLGF, VEGF, and VEGF-B. It can be seen from that figure that the sole glycosylation site of VEGF-A ("NIT") occurs at a position corresponding to residues 65-67 of VEGF-B as numbered in the current specification ("QVR") The VEGF-B of Figure 9 is mouse. At figure 12, mouse and human VEGF-B are aligned, and it can be seen that they are highly similar, and identical in sequence at the position corresponding to the glycosylation site of VEGF-A Recombinant expression of the protein and pharmaceutical compositions comprising the VEGF-B protein are claimed.

Eriksson et al. do not disclose introducing added N-glycosylation into the VEGF-B protein or making nucleic acids encoding such a species, nor do they disclose pharmaceutical compositions comprising heparin and VEGF-B.

Claffey et al. disclose a mutant of VEGF-A in which Asn at residue 74 is replaced with Tyrosine, thus eliminating the sole N-linked glycosylation site in the protein - see Figure 3. At page 7, they state that the activity of the non-glycosylated form was comparable to that of the wild-type, glycosylated form, but that secretion of the non-glycosylated form was only 50% of that of wild-type. Claffey et al. also

Keyt et al. teach variants of VEGF-A. At column 8, they teach that the protein may have N-linked glycosylation sites added to it via recombinant expression of nucleic acids altered to encode such as site, and that N-linked glycosylation may occur at Asn-X-Ser or Asn-X-Thr motifs. Addition of glycosylation sites is also discussed at column 13. At columns 35-36, Keyt

discuss the results of glycosylation-added variants of VEGF-A. They reiterate Claffey's result that elimination of glycosylation at residue 75 did not affect receptor binding. They additionally showed that glycosylation via introduction of a "neoglycosylation site" at residues 42-44 did not interfere with receptor binding, but that glycosylation at residues 82-84 resulted in decreased binding to the KDR receptor, and extra glycosylation at position 64 was shown to decrease Flt-1 but not KDR binding.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify VEGF-B, as taught by Eriksson et al., by introducing a glycosylation site at the position corresponding to the position at which VEGF-A is glycosylated. Such introduction of new glycosylation sites is routine in the art, as taught by Claffey et al. and Keyt et al., and the person of ordinary skill in the art would have been motivated to make the modification in view of Claffey's and Keyt's teachings that glycosylated VEGF-A is secreted better than, and has activity equivalent to, non-glycosylated VEGF-A, and taken in view of Eriksson's alignment of the related proteins, including VEGF-A and VEGF-B, thus pointing out where in VEGF-B the equivalent position is. The possibility of better secretion would be ample motivation to make the change, as such would facilitate recombinant production of the protein. The person of ordinary skill in the art , making this modification, would reasonably have expected the VEGF-B so obtained to retain its biological function, and to be secreted from cells as well or better than non-glycosylated VEGF-B, as that was the result with VEGF-A, a closely related protein. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the cited prior art.

Claims 10 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksson et al. (U.S. Patent Number 5,607,918) in view of Claffey et al. (BBA 1246:1-9, 1995) and Keyt et al. (U.S. Patent Number 6,020,473) as applied to claims 1-9, 11, and 13-18 above, and further in view of Eriksson-2 (U.S. Patent Number 5,840,693) and Chamow et al. (U.S. Patent Number 5,851,989).

Claim 10 recites that the protein composition further comprises heparin, and Claim 12 recites that the host cell expressing the protein is exposed to heparin after the protein is expressed.

Eriksson –2 discloses that treatment of cells expression VEGF-B with heparin results in the release of VEGF-B dimers from the cells, see col. 20, and additionally claims compositions comprising VEGF-B and heparin, see claims 10 and 11.

Chamow et al. disclose that heparin increases the serum half-life of heparin binding proteins such as VEGF; see abstract, and claims.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to treat cells expressing recombinant glycosylated VEGF-B as found obvious above with heparin as taught by Eriksson-2, for the purpose of increasing the yield of secreted dimers, as taught by Eriksson-2.

It would have been further obvious to the person of ordinary skill in the art at the time the invention was made to formulate compositions comprising the glycosylated VEGF-B and heparin as taught by both Eriksson-2 and by Chamow et al., for the purpose of obtaining a pharmaceutical with an extended half-life. One would have been motivated to do so , and would have expected success, in view of the claims of both of the secondary references, and the teachings of the advantages of such as found in the Chamow patent. Accordingly, the claimed subject matter, taken as a whole, is *prima facie* obvious over the prior art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M. ***Effective 1/21/2004, Dr. Spector's telephone number will be 571-272-0893.***

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623. ***Effective 1/21/2004, Dr. Kunz' telephone number will be 571-272-0887.***

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228. ***Effective 1/21/2004, Dr. Spector's fax number will be 571-273-0893.***

Lorraine Spector, Ph.D.
Primary Examiner

1/2/2004